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09/328,975	06/09/1999	JOHN A. WOLFF	MIRUS009	7574
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MIRUS CORPORATION 505 SOUTH ROSA RD MADISON, WI 53719			EXAMINER SCHNIZER, RICHARD A	
			ART UNIT 1635	PAPER NUMBER
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.



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**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

Application Number: 09/328,975  
Filing Date: June 09, 1999  
Appellant(s): WOLFF ET AL.

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Mark K. Johnson  
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed 2/22/07 appealing from the Office action mailed 4/5/06.

**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

**(2) Related Appeals and Interferences**

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**(3) Status of Claims**

The statement of the status of claims contained in the brief is correct.

**(4) Status of Amendments After Final**

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

The summary of claimed subject matter contained in the brief is correct.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

**(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(8) Evidence Relied Upon**

Degols et al (Nucl. Acids Res. 19(4): 945-948, 1991)

Leonetti et al (J. Nat. Cancer Inst. 88(7): 419-429, 1996)

Wiethoff et al (J. Biol. Chem. 276(35): 32806-32813, 2001)

Wu et al (J. Biol. Chem. 269(29): 14621-14624, 1988)

**(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 3, 5, and 7 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Degols et al (Nucl. Acids Res. 19(4): 945-948, 1991) in view of Leonetti et al (J. Nat. Cancer Inst. 88(7): 419-429, 1996), taken with the evidence of Wiethoff et al (J. Biol. Chem. 276(35): 32806-32813, 2001).

Degols taught methods of inhibiting the proliferation of tumor cell in vivo by forming a composition comprising an anti-*c-myc* anti-sense oligonucleotide conjugated to polylysine, and then forming a ternary complex by addition of polyanions such as heparin, carboxymethylcellulose, alginate, and polyglutamate. See abstract; page 946, column 1, first full paragraph, and Fig. 2 at column 2; page 947 column 1, second full paragraph, and Fig. 3; page 947, column 2, second full paragraph. Degols was silent as to the net charge of the ternary complexes.

Evidence that the ternary complexes had a net negative charge is as follows. To form ternary complexes, Degols used polyanions at a concentration of 100 micrograms/ml, and polylysine(PLL)/oligonucleotide conjugates in a range of

Art Unit: 1635

concentrations from 1-2 micromolar. Each oligonucleotide was modified with a PLL molecule at the 3' ribose, so each conjugate contained one molecule of PLL, molecular weight 14000 Da. See page 945, column 2, last full paragraph through page 946, column 1, line 6. Assuming a residue molecular weight of 128.2 Da for lysine, and one positive charge per residue, 14 kDa PLL has a net charge of about 109 positive charges per molecule at physiological pH. The myc oligonucleotides were 17 nucleotides in length, so assuming 1 negative charge per nucleotide, the net charge of each conjugate was about  $109 - 17 = 92$  positive charges. So, if Degols used the conjugates at 1-2 micromolar, this is equivalent to a concentration of positive charges of about 92-184 micromolar.

Wiethoff taught that heparin contains an average of 2.4 sulfates and 1 carboxylate per repeating disaccharide, and that each disaccharide has a molecular weight of 535 Da. See page 32807, column 1, lines 3-8 of the fourth full paragraph. So, heparin has 3.4 moles of negative charge per every 535 g, and it contains 0.64 micromoles of negative charge per 100 micrograms. To form ternary complexes, Degols used heparin at concentration of 100 micrograms/ml, i.e. 0.64 micromoles/ml, or 640 micromolar. Thus, in forming ternary complexes, Degols added negative charges to positive charges at a ratio of 640 micromoles to 92-184 micromoles. Absent evidence to the contrary, this led to the formation of negatively charged ternary complexes.

Degols did not teach a method of delivering the complexes in vivo.

Art Unit: 1635

Leonetti taught a method of delivering anti-*c-myc* anti-sense oligonucleotides to melanoma cells in mice. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the ternary complexes of Degols in the method of Leonetti. One would have been motivated to do so because Degols showed that use of the ternary complexes allowed one to achieve the same anti-proliferative effect with one tenth the amount of oligonucleotide. Compare Figs. 1 and 2 on page 946. Also Degols taught that polyanions inhibit the normal fusion of secondary lysosomes with phagosomes, leading to decreased degradation of endocytosed molecules. See page 948, lines 7-11 of the paragraph bridging columns 1 and 2.

Thus the invention as a whole was prima facie obvious.

The following rejection is made against an embodiment of the claims as newly amended in which there is no covalent linkage between the polycation and the nucleic acid.

Claims 1, 3, 5, and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al (J. Biol. Chem. 269(29): 14621-14624, 1988) in view of Degols et al Nucl. Acids Res. 19(4): 945-948, 1991).

Wu taught formation of ionic complexes of polylysine and DNA and a method of delivering the complexes to cells in vivo. See abstract.

Wu did not teach formation of a complex having a net negative charge by ionically associating a polyanion with the polylysine/DNA complexes.

Art Unit: 1635

The teachings of Degols are discussed above. Degols taught that the toxicity of polylysine in delivery complexes can be reduced by formation of a ternary complex with an excess of polyanions such as heparin, carboxymethylcellulose, alginate, or polyglutamate. See abstract, page 945, column 2, last sentence of first full paragraph.

It would have been obvious to one of ordinary skill in the art at the time of the invention to add a polyanion to the complex of Wu to form a negatively charged ternary complex prior to administration. One would have been motivated to do so to decrease the toxicity of the polylysine as taught by Degols. One could also reasonably expect addition of the polyanions to increase the stability of the complexes against nucleases, as well as to inhibit the maturation of endosomes to lysosomes after uptake of the DNA, thereby facilitating escape of the DNA from endosomes into the cytoplasm. See Degols at page 948, column 1, lines 1-3 and 7-11 of paragraph bridging columns 1 and 2.

Thus the invention as a whole was prima facie obvious.

#### **(10) Response to Argument**

Appellant's arguments filed 2/22/07 have been fully considered but they are not persuasive.

Appellant addresses the rejection over Degols, Leonetti, and Wiethoff at pages 8 and 9 of the response.

Appellant argues that the Degols reference, and the Lemaitre reference cited therein, teach away from the instantly claimed invention. Degols taught a covalent linkage between a polyanionic oligonucleotide and a polycation (polylysine). Appellant

Art Unit: 1635

cites Lemaitre at page 650 to support the position that Degols found it necessary to covalently link the polylysine to the oligonucleotide because the combination of an oligonucleotide and non-covalently linked polylysine did not provide the desired (antiviral) antisense activity. Accordingly, Appellant argues that Degols teaches away from non-covalent associations of antisense oligonucleotides and polycations.

This is unpersuasive because the claims do not exclude the presence of a covalent linkage between the nucleic acid and the polycation, so long as there is also a noncovalent association between the two. In fact, the presence of a covalent linkage only increases the likelihood of a further ionic interaction between the polyanionic oligonucleotide and the polycationic polylysine because it would serve to maintain these two oppositely charged molecules in proximity. Finally, Appellant has provided no evidence that the complexes of Degols lacked such an ionic association.

Clearly one of ordinary skill in the art at the time of the invention understood that complex formation between polycations and polyanions occurred spontaneously in aqueous solution. For example, Degols expected the formation of ternary complexes upon addition of the polyanion heparin to polylysine-oligonucleotide conjugates having a net positive charge. See e.g. legend to Fig. 2 on page 946; page 947, penultimate sentence of column 1; and the rejection above. It follows that one of ordinary skill at the time of the invention would have also expected an ionic interaction to form between polycationic polylysine and a polyanionic oligonucleotide that were already covalently linked. Clearly, covalent linkage between polylysine and a nucleic acid only improves

Art Unit: 1635

the likelihood of obtaining such an ionic interaction because it brings the two oppositely charged ligands into proximity.

Applicant has presented no evidence that the covalent linkage of Degols would prevent, instead of facilitate, a further ionic association between the polycationic polylysine and the polyanionic oligonucleotide. Absent such evidence, the claims read on the ternary complexes of Degols.

Appellant addresses the rejection over Wu in view of Degols at pages 9 and 10 of the Brief.

Appellant reiterates the arguments presented against the rejection over Degols, Leonetti, and Wiethoff, i.e. the Degols reference teaches away from an ionic linkage between a polycation and the polyanion.

This is unpersuasive because, in this rejection, Degols is not relied upon to teach a non-covalent interaction. Wu teaches the non-covalent complex between a nucleic acid and a polycation. Degols is relied upon to teach that:

- a) the toxicity of polylysine in nucleic acid delivery complexes can be reduced by formation of a ternary complex with an excess of a polyanion such as heparin, carboxymethylcellulose, alginate, or polyglutamate,
- b) addition of a polyanion to form a ternary complex with a polycation/nucleic acid complex increases the resistance of the nucleic acid to nucleolytic degradation, and
- c) addition of the excess polyanion will inhibit the maturation of endosomes to lysosomes after uptake of the nucleic acid, thereby facilitating escape of the nucleic acid

Art Unit: 1635

from endosomes into the cytoplasm, thereby avoiding lysosomal degradation of the nucleic acid.

Appellant does not address these motivations for combining the polyanion of Degols with the non-covalent polylysine/nucleic acid complex of Wu, so the rejections are maintained.

**(11) Related Proceeding(s) Appendix**

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

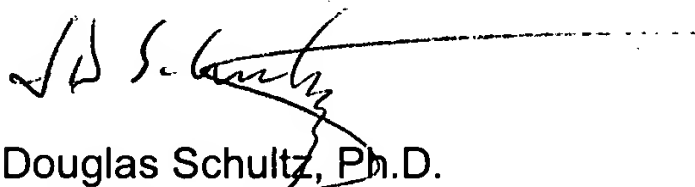
For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

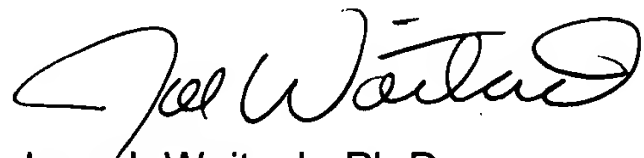


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